

## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>7</sup> : <b>C07D 265/38, A61K 31/538, A61P 3/10, 3/04</b>	<b>A1</b>	(11) International Publication Number: <b>WO 00/63190</b> (43) International Publication Date: 26 October 2000 (26.10.00)
---	-----------	--

(21) International Application Number: PCT/DK00/00189

(22) International Filing Date: 17 April 2000 (17.04.00)

## (30) Priority Data:

PA 1999 00534 20 April 1999 (20.04.99) DK

(71) Applicant: NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK).

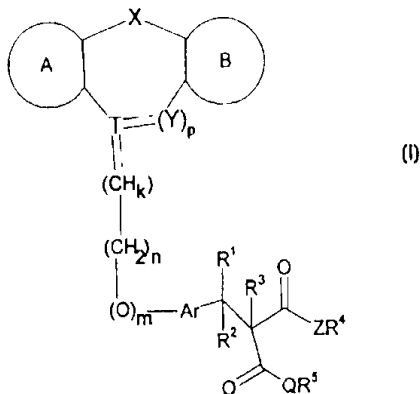
(72) Inventors: JEPPESEN, Lone; Malmlosevej 121, DK-2830 Virum (DK). SAUERBERG, Per; Syrenvænget 27, DK-3520 Farum (DK). MURRAY, Anthony; Esthersvej 32, 1. th., DK-2900 Hellerup (DK). BURY, Paul, Stanley; Hjortholms Allé 48, DK-2400 København NV (DK).

(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

## Published

*With international search report.**Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: NEW COMPOUNDS, THEIR PREPARATION AND USE



## (57) Abstract

The present invention relates to compounds of general formula (I). The compounds are useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

New Compounds, their Preparation and UseFIELD OF INVENTION

5

The present invention relates to novel compounds, pharmaceutical compositions containing them, methods for preparing the compounds and their use as medicaments. More specifically, compounds of the invention can be utilised in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Re-

10 ceptors (PPAR).

BACKGROUND OF THE INVENTION

Coronary artery disease (CAD) is the major cause of death in Type 2 diabetic and metabolic

15 syndrome patients (i.e. patients that fall within the 'deadly quartet' category of impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

The hypolipidaemic fibrates and antidiabetic thiazolidinediones separately display moderately effective triglyceride-lowering activities although they are neither potent nor efficacious

20 enough to be a single therapy of choice for the dyslipidaemia often observed in Type 2 diabetic or metabolic syndrome patients. The thiazolidinediones also potently lower circulating glucose levels of Type 2 diabetic animal models and humans. However, the fibrate class of compounds are without beneficial effects on glycaemia. Studies on the molecular actions of these compounds indicate that thiazolidinediones and fibrates exert their action by activating

25 distinct transcription factors of the peroxisome proliferator activated receptor (PPAR) family, resulting in increased and decreased expression of specific enzymes and apolipoproteins respectively, both key-players in regulation of plasma triglyceride content. Fibrates, on the one hand, are PPAR $\alpha$  activators, acting primarily in the liver. Thiazolidinediones, on the other hand, are high affinity ligands for PPAR $\gamma$  acting primarily on adipose tissue.

30

Adipose tissue plays a central role in lipid homeostasis and the maintenance of energy balance in vertebrates. Adipocytes store energy in the form of triglycerides during periods of nutritional affluence and release it in the form of free fatty acids at times of nutritional deprivation. The development of white adipose tissue is the result of a continuous

35 differentiation process throughout life. Much evidence points to the central role of PPAR $\gamma$

activation in initiating and regulating this cell differentiation. Several highly specialised proteins are induced during adipocyte differentiation, most of them being involved in lipid storage and metabolism. The exact link from activation of PPAR $\gamma$  to changes in glucose metabolism, most notably a decrease in insulin resistance in muscle, has not yet been clarified. A possible link is via free fatty acids such that activation of PPAR $\gamma$  induces Lipoprotein Lipase (LPL), Fatty Acid Transport Protein (FATP) and Acyl-CoA Synthetase (ACS) in adipose tissue but not in muscle tissue. This, in turn, reduces the concentration of free fatty acids in plasma dramatically, and due to substrate competition at the cellular level, skeletal muscle and other tissues with high metabolic rates eventually switch from fatty acid oxidation to glucose oxidation with decreased insulin resistance as a consequence.

PPAR $\alpha$  is involved in stimulating  $\beta$ -oxidation of fatty acids. In rodents, a PPAR $\alpha$ -mediated change in the expression of genes involved in fatty acid metabolism lies at the basis of the phenomenon of peroxisome proliferation, a pleiotropic cellular response, mainly limited to liver and kidney and which can lead to hepatocarcinogenesis in rodents. The phenomenon of peroxisome proliferation is not seen in man. In addition to its role in peroxisome proliferation in rodents, PPAR $\alpha$  is also involved in the control of HDL cholesterol levels in rodents and humans. This effect is, at least partially, based on a PPAR $\alpha$ -mediated transcriptional regulation of the major HDL apolipoproteins, apo A-I and apo A-II. The hypotriglyceridemic action of fibrates and fatty acids also involves PPAR $\alpha$  and can be summarised as follows: (I) an increased lipolysis and clearance of remnant particles, due to changes in lipoprotein lipase and apo C-III levels, (II) a stimulation of cellular fatty acid uptake and their subsequent conversion to acyl-CoA derivatives by the induction of fatty acid binding protein and acyl-CoA synthase, (III) an induction of fatty acid  $\beta$ -oxidation pathways, (IV) a reduction in fatty acid and triglyceride synthesis, and finally (V) a decrease in VLDL production. Hence, both enhanced catabolism of triglyceride-rich particles as well as reduced secretion of VLDL particles constitutes mechanisms that contribute to the hypolipidemic effect of fibrates.

A number of compounds have been reported to be useful in the treatment of hyperglycemia, hyperlipidemia and hypercholesterolemia (U.S. Pat. 5,306,726, PCT Publications nos. W091/19702, WO 95/03038, WO 96/04260, WO 94/13650, WO 94/01420, WO 97/36579, WO 97/25042, WO 95/17394, WO 99/08501, WO 99/19313 and WO 99/16758).

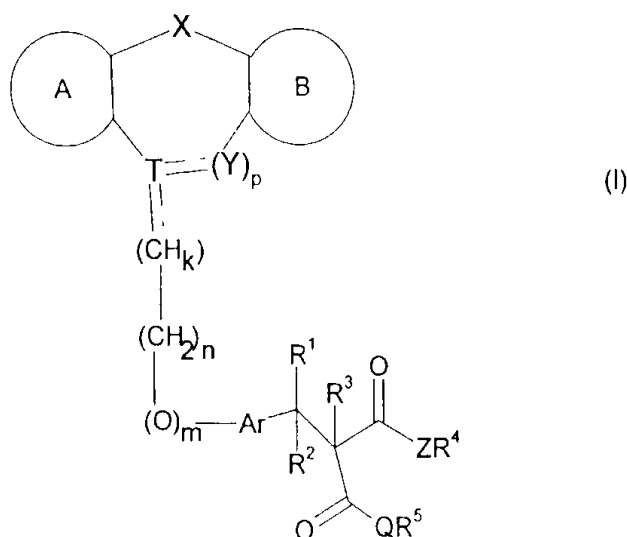
## SUMMARY OF THE INVENTION

Glucose lowering as a single approach does not overcome the macrovascular complications associated with Type 2 diabetes and metabolic syndrome. Novel treatments of Type 2 diabetes and metabolic syndrome must therefore aim at lowering both the overt hypertriglyceridaemia associated with these syndromes as well as alleviation of hyperglycaemia.

The clinical activity of fibrates and thiazolidinediones indicates that research for compounds displaying combined PPAR $\alpha$  and PPAR $\gamma$  activation should lead to the discovery of efficacious glucose and triglyceride lowering drugs that have great potential in the treatment of Type 2 diabetes and the metabolic syndrome (i.e. impaired glucose tolerance, insulin resistance, hypertriglyceridaemia and/or obesity).

### DETAILED DESCRIPTION OF THE INVENTION

Accordingly, the present invention relates to compounds of the general formula (I):



- wherein ring A and ring B, fused to the ring containing X and T, independently of each other represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl, C<sub>1-12</sub>-alkoxy, aryloxy, arylalkyl, arylalkoxy,

- heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC<sub>1-12</sub>-alkyl, amino, acylamino, C<sub>1-12</sub>-alkyl-amino, arylamino, arylalkylamino, amino-C<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkoxycarbonyl, aryloxy, aryloxy, arylalkoxycarbonyl, C<sub>1-12</sub>-alkoxyC<sub>1-12</sub>-alkyl, aryloxyC<sub>1-12</sub>-alkyl, arylalkoxyC<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkylthio, thioC<sub>1-12</sub>-alkyl,
- 5 C<sub>1-12</sub>-alkoxycarbonylamino, aryloxy, aryloxy, arylalkoxycarbonylamino, bicycloalkyl, (C<sub>3-6</sub>-cycloalkyl)C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-dialkylamino, C<sub>1-6</sub>-alkylsulfonyl, C<sub>1-6</sub>-monoalkylaminosulfonyl, C<sub>1-6</sub>-dialkylaminosulfonyl, arylthio, arylsulfonyl, C<sub>1-6</sub>-monoalkylaminocarbonyl, C<sub>1-6</sub>-dialkylaminocarbonyl, -COR<sup>6</sup> or -SO<sub>2</sub>R<sup>7</sup>, wherein R<sup>6</sup> and R<sup>7</sup> independently of each other are selected from hydroxy, halogen,
- 10 perhalomethyl, C<sub>1-6</sub>-alkoxy or amino optionally substituted with one or more C<sub>1-6</sub>-alkyl or perhalomethyl; or aryl, wherein the aryl optionally can be substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or heteroaryl, wherein the heteroaryl optionally can be substituted with halogen, amino hydroxy, C<sub>1-6</sub>-alkyl or C<sub>1-6</sub>-alkoxy; or heterocyclyl, wherein the heterocyclyl optionally can be substituted
- 15 with halogen, amino, hydroxy, C<sub>1-6</sub>-alkyl or C<sub>1-6</sub>-alkoxy;
- X is -O-, -S- or -(NR<sup>8</sup>)- wherein R<sup>8</sup> is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C<sub>1-12</sub>-alkyl-amino, arylamino, arylalkylamino,
- 20 aminoC<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkoxycarbonyl, aryloxy, aryloxy, arylalkoxycarbonyl, C<sub>1-12</sub>-alkoxyC<sub>1-12</sub>-alkyl, aryloxyC<sub>1-12</sub>-alkyl, arylalkoxyC<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkylthio, thioC<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkoxycarbonylamino, aryloxy, aryloxy, arylalkoxycarbonylamino, -COR<sup>9</sup> or -SO<sub>2</sub>R<sup>10</sup>, wherein R<sup>9</sup> and R<sup>10</sup> independently of each other are selected from hydroxy, halogen, C<sub>1-6</sub>-alkoxy, amino optionally substituted with one or more C<sub>1-6</sub>-
- 25 alkyl, perhalomethyl or aryl;
- T is N or CR<sup>14</sup>, wherein R<sup>14</sup> is hydrogen, C<sub>1-12</sub>-alkoxy, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl, aryl or arylalkyl;
- Y is C, O, S, CO, SO, SO<sub>2</sub> or NR<sup>11</sup>, wherein R<sup>11</sup> is hydrogen, C<sub>1-6</sub>-alkyl;

k is 1 or 2;

Ar represents arylene, heteroarylene, or a divalent heterocyclic group each of which can optionally be substituted with one or more halogen, C<sub>1-6</sub>-alkyl, amino, hydroxy, C<sub>1-5</sub>-alkoxy or aryl;

- 5 R<sup>1</sup> represents hydrogen, hydroxy, halogen, C<sub>1-12</sub>-alkoxy, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl or arylalkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- 10 R<sup>2</sup> represents hydrogen, hydroxy, halogen, C<sub>1-12</sub>-alkoxy, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl or arylalkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R<sup>2</sup> forms a bond together with R<sup>3</sup>;

- 15 R<sup>3</sup> represents hydrogen, hydroxy, halogen, C<sub>1-12</sub>-alkoxy, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl, acyl or arylalkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R<sup>3</sup> forms a bond together with R<sup>2</sup>;

- 20 R<sup>4</sup> represents hydrogen, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

R<sup>5</sup> represents hydrogen, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- 25 Z represents oxygen or NR<sup>12</sup>, wherein R<sup>12</sup> represents hydrogen C<sub>1-12</sub>-alkyl, aryl, hydroxyC<sub>1-12</sub>-alkyl or arylalkyl groups or when Z is NR<sup>12</sup>, R<sup>4</sup> and R<sup>12</sup> may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C<sub>1-6</sub>-alkyl;

- 30 Q represents oxygen or NR<sup>13</sup>, wherein R<sup>13</sup> represents hydrogen C<sub>1-12</sub>-alkyl, aryl, hydroxyC<sub>1-12</sub>-alkyl or arylalkyl groups or when Q is NR<sup>13</sup>, R<sup>5</sup> and R<sup>13</sup> may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C<sub>1-6</sub>-alkyl;

n is an integer ranging from 0 to 3;

m is an integer ranging from 0 to 1;

- 35 p is an integer ranging from 0 to 1;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

- 5 In a preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A and ring B, fused to the ring containing X and T independently of each other represents a 5-6 membered cyclic ring, optionally substituted with halogen, C<sub>1-6</sub>-alkyl or aryl, wherein the aryl can be substituted with one or more halogen or C<sub>1-6</sub>-alkyl; or heterocyclyl, wherein the heterocyclyl can be substituted with C<sub>1-6</sub>-alkyl.

10

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A and ring B, fused to the ring containing X and T independently of each other represents a 5-6 membered cyclic ring.

- 15 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein ring A and ring B, fused to the ring containing X and T independently of each other represents aryl.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein X is O.

20

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein T is N.

- 25 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein k is 2.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein  $\text{---}$  represents a single bond.

- 30 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Ar represents arylene.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> represents hydrogen.

35

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein  $R^4$  and  $R^5$  represents hydrogen or methyl.

5 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein Z and Q represents O.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein n is 1.

10 In another preferred embodiment, the present invention is concerned with compounds of formula I wherein m is 1.

In another preferred embodiment, the present invention is concerned with compounds of formula I wherein p is 0.

15

Preferred compounds of the invention are:

2-[4-(2-Phenoxazine-10-yl-ethoxy)-benzyl]-malonic acid dimethyl ester,  
2-[4-(2-Phenoxazine-10-yl-ethoxy)-benzyl]-malonic acid;

20

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

25 In the above structural formulas and throughout the present specification, the following terms have the indicated meaning:

The terms " $C_{1-12}$ -alkyl" as used herein, alone or in combination is intended to include those alkyl groups of the designated length in either a linear or branched or cyclic configuration. represents e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

30 Typical  $C_{1-6}$ -alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, hexyl, iso-hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl and the like.

The terms " $C_{2-n}$ -alkenyl" wherein n' can be from 3 through 15, as used herein, represents an  
35 olefinically unsaturated branched or straight group having from 2 to the specified number of

carbon atoms and at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenyl, 2-propenyl, allyl, iso-propenyl, 1,3-butadienyl, 1-butenyl, hexenyl, pentenyl and the like.

- 5 The terms "C<sub>2-n</sub>-alkynyl" wherein n' can be from 3 through 15, as used herein, represent an unsaturated branched or straight group having from 2 to the specified number of carbon atoms and at least one triple bond. Examples of such groups include, but are not limited to, 1-propynyl, 2-propynyl, 1-butylnyl, 2-butylnyl, 1-pentylnyl, 2-pentylnyl and the like.
- 10 The terms "C<sub>4-n</sub>-alkenynyl" wherein n' can be from 5 through 15, as used herein, represent an unsaturated branched or straight hydrocarbon group having from 4 to the specified number of carbon atoms and both at least one double bond and at least one triple bond. Examples of such groups include, but are not limited to, 1-penten-4-yne, 3-penten-1-yne, 1,3-hexadiene-5-yne and the like.
- 15 The term "C<sub>1-12</sub>-alkoxy" as used herein, alone or in combination is intended to include those C<sub>1-12</sub>-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy, hexoxy and the like.
- 20 Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, isohexoxy and the like. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy and the like.
- The term "C<sub>1-12</sub>-alkylthio" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C<sub>1-12</sub>-alkyl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom and having 1 to 12 carbon atoms e.g. methylthio, ethylthio, propylthio, butylthio, pentylthio and the like. Examples of cyclic alkylthio are cyclopropylthio, cyclobutylthio, cyclopentylthio, cyclohexylthio and the like.
- 30 The term "C<sub>1-12</sub>-alkylamino" as used herein, alone or in combination, refers to a straight or branched or cyclic monovalent substituent comprising a C<sub>1-12</sub>-alkyl group linked through amino having a free valence bond from the nitrogen atom e.g. methylamino, ethylamino, propylamino, butylamino, pentylamino and the like. Examples of cyclic alkylamino are cyclopropylamino, cyclobutylamino, cyclopentylamino, cyclohexylamino and the like.
- 35

The term "hydroxyC<sub>1-12</sub>-alkyl" as used herein, alone or in combination, refers to a C<sub>1-12</sub>-alkyl as defined herein whereto is attached a hydroxy group, e.g. hydroxyethyl, 1-hydroxypropyl, 2-hydroxypropyl and the like.

5

The term "arylamino" as used herein, alone or in combination, refers to an aryl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. phenylamino, naphthylamino and the like.

10 The term "arylalkylamino" as used herein, alone or in combination, refers to an arylalkyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzylamino, phenethylamino, 3-phenylpropylamino, 1-naphthylmethylamino, 2-(1-naphthyl)ethylamino and the like.

15 The term "aminoC<sub>1-12</sub>-alkyl" as used herein, alone or in combination, refers to a C<sub>1-12</sub>-alkyl as defined herein whereto is attached an amino group, e.g. aminoethyl, 1-aminopropyl, 2-aminopropyl and the like.

The term "aryloxycarbonyl" as used herein, alone or in combination, refers to an aryloxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. phenoxycarbonyl, 1-naphthyloxycarbonyl or 2-naphthyloxycarbonyl and the like.

25 The term "arylalkoxycarbonyl" as used herein, alone or in combination, refers to an arylalkoxy as defined herein linked through a carbonyl having a free valence bond from the carbon atom, e.g. benzyloxycarbonyl, phenethoxycarbonyl, 3-phenylpropoxycarbonyl, 1-naphthylmethoxycarbonyl, 2-(1-naphthyl)ethoxycarbonyl and the like.

30 The term "C<sub>1-12</sub>-alkoxyC<sub>1-12</sub>-alkyl" as used herein, alone or in combination, refers to a C<sub>1-12</sub>-alkyl as defined herein whereto is attached a C<sub>1-12</sub>-alkoxy as defined herein, e.g. methoxymethyl, ethoxymethyl, methoxyethyl, ethoxyethyl and the like.

The term "aryloxyC<sub>1-12</sub>-alkyl" as used herein, alone or in combination, refers to a C<sub>1-12</sub>-alkyl as defined herein whereto is attached an aryloxy as defined herein, e.g. phenoxymethyl, phenoxydodecyl, 1-naphthyloxyethyl, 2-naphthyloxypropyl and the like.

35

The term "arylalkoxyC<sub>1-12</sub>-alkyl" as used herein, alone or in combination, refers to a C<sub>1-12</sub>-alkyl as defined herein whereto is attached an arylalkoxy as defined herein, e.g. benzyloxymethyl, phenethoxydodecyl, 3-phenylpropoxyethyl, 1-naphthylmethoxypropyl, 2-(1-naphthyl)ethoxymethyl and the like.

5

The term "thioC<sub>1-12</sub>-alkyl" as used herein, alone or in combination, refers to a C<sub>1-12</sub>-alkyl as defined herein whereto is attached a group of formula -SR<sup>'''</sup> wherein R<sup>'''</sup> is hydrogen, C<sub>1-6</sub>-alkyl or aryl, e.g. thiomethyl, methylthiomethyl, phenylthioethyl and the like.

10 The term "C<sub>1-12</sub>-alkoxycarbonylamino" as used herein, alone or in combination, refers to a C<sub>1-12</sub>-alkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. methoxycarbonylamino, carbethoxyamino, propoxycarbonylamino, isopropoxycarbonylamino, n-butoxycarbonylamino, tert-butoxycarbonylamino and the like.

15 The term "aryloxycarbonylamino" as used herein, alone or in combination, refers to an aryloxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. phenoxycarbonylamino, 1-naphthylloxycarbonylamino or 2-naphthylloxycarbonylamino and the like.

20 The term "arylalkoxycarbonylamino" as used herein, alone or in combination, refers to an arylalkoxycarbonyl as defined herein linked through amino having a free valence bond from the nitrogen atom e.g. benzyloxycarbonylamino, phenethoxycarbonylamino, 3-phenylpropoxycarbonylamino, 1-naphthylmethoxycarbonylamino, 2-(1-naphthyl)ethoxycarbonylamino and the like.

25

The term "aryl" is intended to include aromatic rings, such as carboxylic aromatic rings selected from the group consisting of phenyl, naphthyl, (1-naphthyl or 2-naphthyl) and the like optionally substituted with halogen, amino, hydroxy, C<sub>1-6</sub>-alkyl or C<sub>1-6</sub>-alkoxy and the like.

30 The term "arylene" is intended to include divalent aromatic rings, such as carboxylic aromatic rings selected from the group consisting of phenylene, naphthylene and the like optionally substituted with halogen, amino, hydroxy, C<sub>1-6</sub>-alkyl or C<sub>1-6</sub>-alkoxy and the like.

The term "halogen" means fluorine, chlorine, bromine or iodine.

35

The term "perhalomethyl" means trifluoromethyl, trichloromethyl, tribromomethyl or triiodomethyl.

5 The term "C<sub>1-6</sub>-dialkylamino" as used herein refers to an amino group wherein the two hydrogen atoms independently are substituted with a straight or branched, saturated hydrocarbon chain having the indicated number of carbon atoms; such as dimethylamino, N-ethyl-N-methylamino, diethylamino, dipropylamino, N-(n-butyl)-N-methylamino, di(n-pentyl)amino and the like.

10 The term "acyl" as used herein refers to a monovalent substituent comprising a C<sub>1-6</sub>-alkyl group linked through a carbonyl group; such as e.g. acetyl, propionyl, butyryl, isobutyryl, pivaloyl, valeryl and the like.

The term "acyloxy" as used herein refers to acyl as defined herein linked to an oxygen atom  
15 having its free valence bond from the oxygen atom e.g. acetyloxy, propionyloxy, butyryloxy, isobutyryloxy, pivaloyloxy, valeryloxy and the like.

The term "C<sub>1-12</sub>-alkoxycarbonyl" as used herein refers to a monovalent substituent  
20 comprising a C<sub>1-12</sub>-alkoxy group linked through a carbonyl group; such as e.g. methoxycarbonyl, carbethoxy, propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, sec-butoxycarbonyl, tert-butoxycarbonyl, 3-methylbutoxycarbonyl, n-hexoxycarbonyl and the like.

The term "bicycloalkyl" as used herein refers to a monovalent substituent comprising a  
25 bicyclic structure made of 6-12 carbon atoms such as e.g. 2-norbornyl, 7-norbornyl, 2-bicyclo[2.2.2]octyl and 9-bicyclo[3.3.1]nonanyl and the like.

The term "heteroaryl" as used herein, alone or in combination, refers to a monovalent substituent comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered  
30 bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine and the like.

The term "heteroarylene" as used herein, alone or in combination, refers to a divalent group comprising a 5-6 membered monocyclic aromatic system or a 9-10 membered bicyclic aromatic system containing one or more heteroatoms selected from nitrogen, oxygen and sulfur, e.g. furan, thiophene, pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine and the like.

The term "heteroaryloxy" as used herein, alone or in combination, refers to a heteroaryl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom e.g. pyrrole, imidazole, pyrazole, triazole, pyridine, pyrazine, pyrimidine, pyridazine, isothiazole, isoxazole, oxazole, oxadiazole, thiadiazole, quinoline, isoquinoline, quinazoline, quinoxaline, indole, benzimidazole, benzofuran, pteridine and purine linked to oxygen, and the like.

The term "arylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic carbohydride; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphthylmethyl, 2-(1-naphthyl)ethyl and the like.

The term "aryloxy" as used herein refers to phenoxy, 1-naphthoxy, 2-naphthoxy and the like.

The term "arylalkoxy" as used herein refers to a C<sub>1-6</sub>-alkoxy group substituted with an aromatic carbohydride, such as benzyloxy, phenethoxy, 3-phenylpropoxy, 1-naphthylmethoxy, 2-(1-naphthyl)ethoxy and the like.

The term "heteroarylalkyl" as used herein refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with a heteroaryl group; such as (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl and the like.

The term "heteroarylalkoxy" as used herein refers to a heteroarylalkyl as defined herein linked to an oxygen atom having its free valence bond from the oxygen atom, e.g. (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, 1-methyl-1-(2-pyrimidyl)ethyl linked to oxygen, and the like.

The term "C<sub>1-6</sub>-alkylsulfonyl" as used herein refers to a monovalent substituent comprising a C<sub>1-6</sub>-alkyl group linked through a sulfonyl group such as e.g. methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, sec-butylsulfonyl, isobutylsulfonyl, tert-butylsulfonyl, n-pentylsulfonyl, 2-methylbutylsulfonyl, 3-methylbutylsulfonyl, n-hexylsulfonyl, 4-methylpentylsulfonyl, neopentylsulfonyl, n-hexylsulfonyl, 2,2-dimethylpropylsulfonyl and the like.

The term "C<sub>1-6</sub>-monoalkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C<sub>1-6</sub>-monoalkylamino group linked through a sulfonyl group such as e.g. methylaminosulfonyl, ethylaminosulfonyl, n-propylaminosulfonyl, isopropylaminosulfonyl, n-butylaminosulfonyl, sec-butylaminosulfonyl, isobutylaminosulfonyl, tert-butylaminosulfonyl, n-pentylaminosulfonyl, 2-methylbutylaminosulfonyl, 3-methylbutylaminosulfonyl, n-hexylaminosulfonyl, 4-methylpentylaminosulfonyl, neopentylaminosulfonyl, n-hexylaminosulfonyl, 2,2-dimethylpropylaminosulfonyl and the like.

The term "C<sub>1-6</sub>-dialkylaminosulfonyl" as used herein refers to a monovalent substituent comprising a C<sub>1-6</sub>-dialkylamino group linked through a sulfonyl group such as dimethylaminosulfonyl, N-ethyl-N-methylaminosulfonyl, diethylaminosulfonyl, dipropylaminosulfonyl, N-(n-butyl)-N-methylaminosulfonyl, di(n-pentyl)aminosulfonyl and the like.

The term "acylamino" as used herein refers to an amino group wherein one of the hydrogen atoms is substituted with an acyl group, such as e.g. acetamido, propionamido, isopropylcarbonylamino and the like.

The term "(C<sub>3-6</sub>-cycloalkyl)C<sub>1-6</sub>-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1 to 6 carbon atoms and being monosubstituted with a C<sub>3-6</sub>-cycloalkyl group, the cycloalkyl group optionally being mono- or polysubstituted with C<sub>1-6</sub>-alkyl, halogen, hydroxy or C<sub>1-6</sub>-alkoxy; such as e.g. cyclopropylmethyl, (1-methylcyclopropyl)methyl, 1-(cyclopropyl)ethyl, cyclopentylmethyl, cyclohexylmethyl and the like.

The term "arylthio" as used herein, alone or in combination, refers to an aryl group linked through a divalent sulfur atom having its free valence bond from the sulfur atom, the aryl group

optionally being mono- or polysubstituted with C<sub>1-6</sub>-alkyl, halogen, hydroxy or C<sub>1-6</sub>-alkoxy; e.g. phenylthio, (4-methylphenyl)-thio, (2-chlorophenyl)thio and the like.

5 The term "arylsulfonyl" as used herein refers to an aryl group linked through a sulfonyl group, the aryl group optionally being mono- or polysubstituted with C<sub>1-6</sub>-alkyl, halogen, hydroxy or C<sub>1-6</sub>-alkoxy; such as e.g. phenylsulfonyl, tosyl and the like.

10 The term "C<sub>1-6</sub>-monoalkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C<sub>1-6</sub>-monoalkylamino group linked through a carbonyl group such as e.g. methylaminocarbonyl, ethylaminocarbonyl, n-propylaminocarbonyl, isopropylaminocarbonyl, n-butylaminocarbonyl, sec-butylaminocarbonyl, isobutylaminocarbonyl, tert-butylaminocarbonyl, n-pentylaminocarbonyl, 2-methylbutylaminocarbonyl, 3-methylbutylaminocarbonyl, n-hexylaminocarbonyl, 4-methylpentylaminocarbonyl, neopentylaminocarbonyl, n-hexylaminocarbonyl, 2-2-dimethylpropylaminocarbonyl and the like.

15 The term "C<sub>1-6</sub>-dialkylaminocarbonyl" as used herein refers to a monovalent substituent comprising a C<sub>1-6</sub>-dialkylamino group linked through a carbonyl group such as dimethylaminocarbonyl, N-ethyl-N-methylaminocarbonyl, diethylaminocarbonyl, dipropylaminocarbonyl, N-(n-butyl)-N-methylaminocarbonyl, di(n-pentyl)aminocarbonyl and the like.

20 As used herein, the phrase "heterocyclyl" means a monovalent saturated or unsaturated non aromatic group being monocyclic and containing one or more, such as from one to four carbon atom(s), and from one to four N, O or S atom(s) or a combination thereof. The phrase "heterocyclyl" includes, but is not limited to, 5-membered heterocycles having one heteroatom (e.g. pyrrolidine, pyrroline and the like); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone and the like); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofurazan and the like); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine and the like); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine and the like); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms, and the like.

35 As used herein, the phrase "a divalent heterocyclic group" means a divalent saturated or unsaturated system being monocyclic and containing one or more, such as from one to four

carbon atom(s), and one to four N, O or S atom(s) or a combination thereof. The phrase a divalent heterocyclic group includes, but is not limited to, 5-membered heterocycles having one hetero atom (e.g. pyrrolidine, pyrroline and the like); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. pyrazoline, pyrazolidine, 1,2-oxathiolane, imidazolidine, imidazoline, 4-oxazolone and the like); 5-membered heterocycles having three heteroatoms (e.g. tetrahydrofuran and the like); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. piperidine and the like); 6-membered heterocycles with two heteroatoms (e.g. piperazine, morpholine and the like); 6-membered heterocycles with three heteroatoms; and 6-membered heterocycles with four heteroatoms, and the like.

As used herein, the phrase "a 5-6 membered cyclic ring" means an unsaturated or saturated or aromatic system containing one or more carbon atoms and optionally from one to four N, O or S atom(s) or a combination thereof. The phrase "a 5-6 membered cyclic ring" includes, but is not limited to, e.g. cyclopentyl, cyclohexyl, phenyl, cyclohexenyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, pyrazolidinyl, pyrazolinyl, piperidyl, piperazinyl, pyrrolyl, 2H-pyrrolyl, imidazolyl, pyrazolyl, triazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiomorpholinyl, isothiazolyl, isoxazolyl, oxazolyl, oxadiazolyl, thiadiazolyl, 1,3-dioxolanyl, 1,4-dioxolanyl and the like, 5-membered heterocycles having one hetero atom (e.g. thiophenes, pyrroles, furans and the like); 5-membered heterocycles having two heteroatoms in 1,2 or 1,3 positions (e.g. oxazoles, pyrazoles, imidazoles, thiazoles, purines and the like); 5-membered heterocycles having three heteroatoms (e.g. triazoles, thiadiazoles and the like); 5-membered heterocycles having four heteroatoms; 6-membered heterocycles with one heteroatom (e.g. pyridine, quinoline, isoquinoline, phenanthridine, cyclohepta[b]pyridine and the like); 6-membered heterocycles with two heteroatoms (e.g. pyridazines, cinnolines, phthalazines, pyrazines, pyrimidines, quinazolines, morpholines and the like); 6-membered heterocycles with three heteroatoms (e.g. 1,3,5-triazine and the like); and 6-membered heterocycles with four heteroatoms and the like.

Certain of the above defined terms may occur more than once in the above formula (I), and upon such occurrence each term shall be defined independently of the other.

The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium

and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sulphates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthoates, glycerophosphates, ketoglutarates and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977, 66, 2, which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like. Examples of ammonium and alkylated ammonium salts include ammonium, methylammonium, dimethylammonium, trimethylammonium, ethylammonium, hydroxyethylammonium, diethylammonium, butylammonium, tetramethylammonium salts and the like. Examples of organic bases include lysine, arginine, guanidine, diethanolamine, choline and the like.

The pharmaceutically acceptable salts are prepared by reacting the compound of formula I with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium t-butoxide, calcium hydroxide, magnesium hydroxide and the like, in solvents like ether, THF, methanol, t-butanol, dioxane, isopropanol, ethanol etc. Mixture of solvents may be used. Organic bases like lysine, arginine, diethanolamine, choline, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, p-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, tartaric acid and the like in solvents like ethyl acetate, ether, alcohols, acetone, THF, dioxane etc. Mixture of solvents may also be used.

The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred meth-

ods include use of microbial resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, lactic acid, and the like wherever applicable or chiral bases such as brucine, cinchona alkaloids and their derivatives and the like. Commonly used methods are compiled by Jaques et al in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of formula I may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, amino acids, amino alcohols derived from amino acids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula I may be prepared by hydrolysing the pure diastereomeric amide.

Various polymorphs of compound of general formula I forming part of this invention may be prepared by crystallization of compound of formula I under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization; crystallizations at different temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe nmr spectroscopy, ir spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

Furthermore, the present compounds of formula I can be utilised in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

In a further aspect, the present invention relates to a method of treating and/or preventing Type I or Type II diabetes.

In a still further aspect, the present invention relates to the use of one or more compounds of the general formula I or pharmaceutically acceptable salts thereof for the preparation of a medicament for the treatment and/or prevention of Type I or Type II diabetes.

5

In a still further aspect, the present compounds are useful for the treatment and/or prevention of IGT.

10

In a still further aspect, the present compounds are useful for the treatment and/or prevention of Type 2 diabetes.

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from IGT to Type 2 diabetes.

15

In a still further aspect, the present compounds are useful for the delaying or prevention of the progression from non-insulin requiring Type 2 diabetes to insulin requiring Type 2 diabetes.

20

In another aspect, the present compounds reduce blood glucose and triglyceride levels and are accordingly useful for the treatment and/or prevention of ailments and disorders such as diabetes and/or obesity.

25

In still another aspect, the present compounds are useful for the treatment and/or prophylaxis of insulin resistance (Type 2 diabetes), impaired glucose tolerance, dyslipidemia, disorders related to Syndrome X such as hypertension, obesity, insulin resistance, hyperglycaemia, atherosclerosis, hyperlipidemia, coronary artery disease, myocardial ischemia and other cardiovascular disorders.

30

In still another aspect, the present compounds are effective in decreasing apoptosis in mammalian cells such as beta cells of Islets of Langerhans.

In still another aspect, the present compounds are useful for the treatment of certain renal diseases including glomerulonephritis, glomerulosclerosis, nephrotic syndrome, hypertensive nephrosclerosis.

35

In still another aspect, the present compounds may also be useful for improving cognitive functions in dementia, treating diabetic complications, psoriasis, polycystic ovarian syndrome (PCOS) and prevention and treatment of bone loss, e.g. osteoporosis.

- 5 The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound of the formula I or any optical or geometric isomer or tautomeric form thereof including mixtures of these or a pharmaceutically acceptable salt thereof together with one or more pharmaceutically acceptable carriers or diluents.
- 10 Furthermore, the invention relates to the use of compounds of the general formula I or their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates thereof for the preparation of a pharmaceutical composition for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR) such as the conditions
- 15 mentioned above.

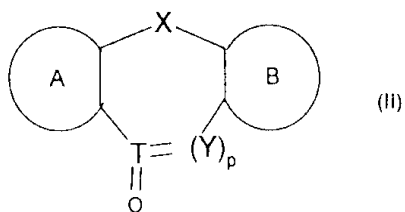
The present invention also relates to a process for the preparation of the above said novel compounds, their derivatives, their analogs, their tautomeric forms, their stereoisomers, their polymorphs, their pharmaceutically acceptable salts or pharmaceutically acceptable solvates.

20

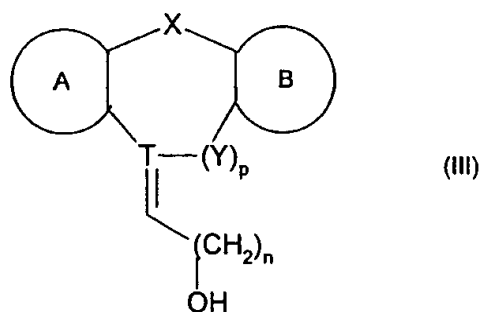
A compound of formula I can be prepared as described below:

- a) Reacting a compound of formula II, wherein A, B, T, X, Y, and p are as defined previously, except that T is not N,

25

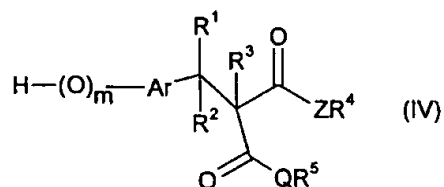


- through a Wittig process with  $(\text{PH}_3\text{P})_3\text{P}(\text{CH}_2)_{n+1}\text{OH.Br}$  in the presence of a suitable base as
- 30 butyllithium, to give compounds of formula III.



wherein A, B, X, Y, T, p and n are defined as previously, except that T is not N. Compounds of formula III may then be reacted under Mitsunobu conditions with compounds of formula IV

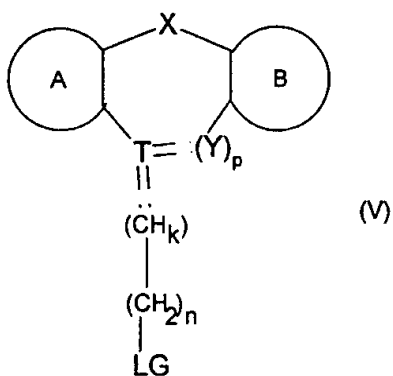
5



wherein m, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> are defined as previously and wherein R<sup>4</sup> and R<sup>5</sup> are defined as previously except H, to give compounds of formula I, wherein A, B, X, Y, T, Ar, Z, Q, p, n, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> are defined as previously, except that T is not N, and wherein R<sup>4</sup> and R<sup>5</sup> are defined as previously except H, and wherein m and k is 1 and within the term T==(Y)<sub>p</sub>, == is defined as a single bond and within the term T==(CH<sub>k</sub>), == is defined as a double bond.

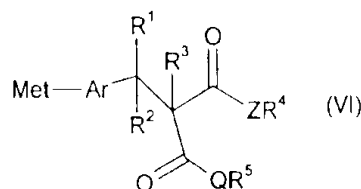
10

b) Alternatively a compound of formula V



15

wherein A, B, X, Y, T, p, n, k and the terms  $T==(Y)_p$  and  $T==(CH_k)$  are defined as previously and wherein LG is a suitable leaving group, may be reacted, possible under transition metal catalysis, with a nucleophilic compound of formula VI



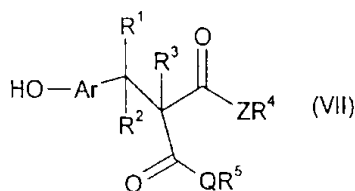
5

wherein Ar,  $R^1$ ,  $R^2$ ,  $R^3$  are defined as previously and wherein  $R^4$  and  $R^5$  are defined as previously except H and wherein "Met" is a metal such as zinc or copper, carrying suitable ligands preferentially from trifluoro-methanesulfonate or halide to give compounds of formula I,

10 wherein A, B, X, Y, T, Ar, Z, Q, p, n,  $R^1$ ,  $R^2$ ,  $R^3$ , and the terms  $T==(Y)_p$  and  $T==(CH_k)$  are defined as previously and wherein  $R^4$  and  $R^5$  are defined as previously except H, and wherein m is 0.

c) Alternatively compounds of formula V wherein A, B, X, Y, T, p, n, and the terms  $T==(Y)_p$  and  $T==(CH_k)$  are defined as previously and wherein LG is a suitable leaving group (for example halogen, sulfonates, phosphor, hydroxy under Mitsunobu conditions) are reacted with a compound of VII

15

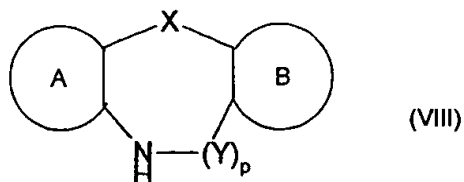


20

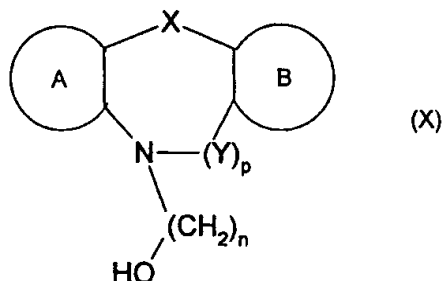
wherein Ar, Z, Q,  $R^1$ ,  $R^2$ ,  $R^3$  are defined as previously and wherein  $R^4$  and  $R^5$  are defined as previously except H, to give compounds of formula I, wherein A, B, X, Y, T, Ar, Z, Q, p, n,  $R^1$ ,  $R^2$ ,  $R^3$ , and the terms  $T==(Y)_p$  and  $T==(CH_k)$  are defined as previously and wherein  $R^4$  and  $R^5$  are defined as previously except H, and wherein m is 1.

25

d) Alternatively a compound of formula VIII

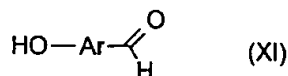


- wherein A, B, X, Y and p are defined as previously, may be alkylated with a suitable electrophilic reagent such as ethylene oxide, ethyl bromoacetate followed by reduction of the ester to an alcohol, 2-bromoethanol or 2-bromoethanol to give a compound of formula X

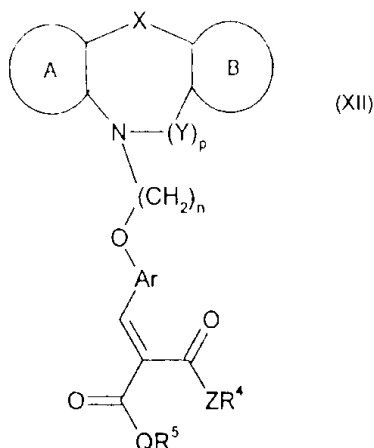


- wherein A, B, X, Y, p and n are defined as previously. The hydroxy group can if needed be converted to a suitable leaving group and reacted with a compound of formula VII, wherein Ar, Z, Q, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> are defined as previously and wherein R<sup>4</sup> and R<sup>5</sup> are defined as previously except H, to give compounds of formula I, wherein A, B, X, Y, Ar, Z, Q, p, n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are defined as previously and within the terms T==(Y)<sub>p</sub> and T==(CH<sub>k</sub>), == is defined as a singlebond and wherein R<sup>4</sup> and R<sup>5</sup> are defined as previously except H, and wherein m is 1 and k is 0 and wherein T is N.

- e) Alternatively reacting compounds of formula X wherein A, B, X, Y, p and n are defined as previously, with a compound of formula XI



- wherein Ar is defined as previously, followed by reaction with a suitable Wittig reagent to give a compound of formula XII



- 5 wherein A, B, X, Y, Ar, Z, Q, p, n, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and the terms T==(Y)<sub>p</sub> and T==(CH)<sub>k</sub> are defined as previously and wherein R<sup>4</sup> and R<sup>5</sup> are defined as previously except H. Addition to the double bond of suitable reagents give compounds of formula I, wherein A, B, X, Y, Ar, Z, Q, p, n, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are defined as previously and within the terms T==(Y)<sub>p</sub> and T==(CH)<sub>k</sub>, == is defined as a single bond and wherein R<sup>4</sup> and R<sup>5</sup> are defined as previously except H, and
- 10 wherein m is 1 and k is 0 and wherein T is N.

- f) Alternatively compounds of formula I wherein A, B, X, Y, T, Ar, p, n, k, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and the terms T==(Y)<sub>p</sub> and T==(CH)<sub>k</sub> are defined as previously and wherein Z and Q is O and wherein R<sup>4</sup> and R<sup>5</sup> are defined as previously except H can either be hydrolysed to the corresponding acid or be reacted further to give a compound of formula I wherein A, B, X, Y, T, Ar,
- 15 Z, Q, p, n, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup> and the terms T==(Y)<sub>p</sub> and T==(CH)<sub>k</sub> are defined as previously.

## PHARMACOLOGICAL METHODS

20

### **In vitro PPAR alpha and PPAR gamma activation activity.**

#### Principle

- 25 The PPAR gene transcription activation assays were based on transient transfection into human HEK293 cells of two plasmids encoding a chimeric test protein and a reporter protein

respectively. The chimeric test protein was a fusion of the DNA binding domain (DBD) from the yeast GAL4 transcription factor to the ligand binding domain (LBD) of the human PPAR proteins. The PPAR LBD harbored in addition to the ligand binding pocket also the native activation domain (activating function 2 = AF2) allowing the fusion protein to function as a PPAR ligand dependent transcription factor. The GAL4 DBD will force the fusion protein to bind only to Gal4 enhancers (of which none existed in HEK293 cells). The reporter plasmid contained a Gal4 enhancer driving the expression of the firefly luciferase protein. After transfection, HEK293 cells expressed the GAL4-DBD-PPAR-LBD fusion protein. The fusion protein will in turn bind to the Gal4 enhancer controlling the luciferase expression, and do nothing in the absence of ligand. Upon addition to the cells of a PPAR ligand, luciferase protein will be produced in amounts corresponding to the activation of the PPAR protein. The amount of luciferase protein is measured by light emission after addition of the appropriate substrate.

## 15 Methods

Cell culture and transfection: HEK293 cells were grown in DMEM + 10% FCS, 1% PS. Cells were seeded in 96-well plates the day before transfection to give a confluency of 80 % at transfection. 0,8 µg DNA per well was transfected using FuGene transfection reagent according to the manufacturers instructions (Boehringer-Mannheim). Cells were allowed to express protein for 48 h followed by addition of compound.

Plasmids: Human PPAR  $\alpha$  and  $\gamma$  was obtained by PCR amplification using cDNA templates from liver, intestine and adipose tissue respectively. Amplified cDNAs were cloned into pCR2.1 and sequenced. The LBD from each isoform PPAR was generated by PCR (PPAR $\alpha$ : aa 167 - C-term; PPAR $\gamma$ : aa 165 - C-term) and fused to GAL4-DBD by subcloning fragments in frame into the vector pM1 generating the plasmids pM1 $\alpha$ LBD and pM1 $\gamma$ LBD. Ensuing fusions were verified by sequencing. The reporter was constructed by inserting an oligonucleotide encoding five repeats of the Gal4 recognition sequence into the pGL2 vector (Promega).

Compounds: All compounds were dissolved in DMSO and diluted 1:1000 upon addition to the cells. Cells were treated with compound (1:1000 in 200 µl growth medium including delipidated serum) for 24 h followed by luciferase assay.

Luciferase assay: Medium including test compound was aspirated and 100  $\mu$ l PBS incl. 1mM  $Mg^{++}$  and  $Ca^{++}$  was added to each well. The luciferase assay was performed using the LucLite kit according to the manufacturers instructions (Packard Instruments). Light emission was quantified by counting SPC mode on a Packard Instruments top-counter.

5

#### PHARMACEUTICAL COMPOSITIONS

10 In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

15 The present compounds may also be administered in combination with one or more further pharmacologically active substances eg. selected from antiobesity agents, antidiabetics, antihypertensive agents, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

20

Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists,  $\beta 3$  agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyreotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, RXR (retinoid X receptor) modulators or TR  $\beta$  agonists.

35

In one embodiment of the invention the antiobesity agent is leptin.

In another embodiment the antiobesity agent is dexamphetamine or amphetamine.

5

In another embodiment the antiobesity agent is fenfluramine or dexfenfluramine.

In still another embodiment the antiobesity agent is sibutramine.

10 In a further embodiment the antiobesity agent is orlistat.

In another embodiment the antiobesity agent is mazindol or phentermine.

15 Suitable antidiabetics comprise insulin, GLP-1 (glucagon like peptide-1) derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycaemic agents.

20 The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03861 to Novo Nordisk A/S which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such  
25 as antihyperlipidemic agents and antilipidemic agents as HMG CoA inhibitors (statins), compounds lowering food intake, RXR agonists and agents acting on the ATP-dependent potassium channel of the  $\beta$ -cells.

30 In one embodiment of the invention the present compounds are administered in combination with insulin.

In a further embodiment the present compounds are administered in combination with a sulphonylurea eg. tolbutamide, glibenclamide, glipizide or glicazide.

In another embodiment the present compounds are administered in combination with a biguanide eg. metformin.

In yet another embodiment the present compounds are administered in combination with a  
5 meglitinide eg. repaglinide.

In a further embodiment the present compounds are administered in combination with an  $\alpha$ -glucosidase inhibitor eg. miglitol or acarbose.

10 In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the  $\beta$ -cells eg. tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

Furthermore, the present compounds may be administered in combination with nateglinide.  
15

In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent eg. cholestyramine, colestipol, clofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, probucol or dextrothyroxine.

20 In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds eg. in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin, insulin and lovastatin, etc.

25 Furthermore, the present compounds may be administered in combination with one or more antihypertensive agents. Examples of antihypertensive agents are  $\beta$ -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol and metoprolol, ACE (angiotensin converting enzyme) inhibitors such as benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and ramipril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, ni-  
30 modipine, diltiazem and verapamil, and  $\alpha$ -blockers such as doxazosin, urapidil, prazosin and terazosin. Further reference can be made to Remington: The Science and Practice of Pharmacy, 19<sup>th</sup> Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

It should be understood that any suitable combination of the compounds according to the in-  
35 vention with one or more of the above-mentioned compounds and optionally one or more fur-

ther pharmacologically active substances are considered to be within the scope of the present invention.

Pharmaceutical compositions containing a compound of the present invention may be prepared  
5 by conventional techniques, e.g. as described in Remington: The Science and Practise of  
Pharmacy, 19<sup>th</sup> Ed., 1995. The compositions may appear in conventional forms, for example  
capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include a compound of formula I or a pharmaceutically acceptable acid  
10 addition salt thereof, associated with a pharmaceutically acceptable excipient which may be  
a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in  
the form of a capsule, sachet, paper or other container. In making the compositions,  
conventional techniques for the preparation of pharmaceutical compositions may be used.  
For example, the active compound will usually be mixed with a carrier, or diluted by a carrier,  
15 or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper,  
or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid  
material which acts as a vehicle, excipient, or medium for the active compound. The active  
compound can be adsorbed on a granular solid container for example in a sachet. Some  
examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols,  
20 polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose,  
cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or  
lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid  
monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene,  
hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include  
25 any sustained release material known in the art, such as glyceryl monostearate or glyceryl  
distearate, alone or mixed with a wax. The formulations may also include wetting agents,  
emulsifying and suspending agents, preserving agents, sweetening agents or flavouring  
agents. The formulations of the invention may be formulated so as to provide quick,  
sustained, or delayed release of the active ingredient after administration to the patient by  
30 employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary  
agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring sub-  
stances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment, the oral route being preferred.

5

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

10

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

15

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

20

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

25

A typical tablet which may be prepared by conventional tableting techniques may contain:

Core:

Active compound (as free compound or salt thereof)	5 mg
30 Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	Ad.

35 Coating:

HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

\*Acylated monoglyceride used as plasticizer for film coating.

5

The compounds of the invention may be administered to a mammal, especially a human in need of such treatment, prevention, elimination, alleviation or amelioration of diseases related to the regulation of blood sugar.

Such mammals include also animals, both domestic animals, e.g. household pets, and non-domestic animals such as wildlife.

10

The compounds of the invention are effective over a wide dosage range. For example, in the treatment of adult humans, dosages from about 0.05 to about 100 mg, preferably from about 0.1 to about 100 mg, per day may be used. A most preferable dosage is about 0.1 mg to about 70 mg per day. In choosing a regimen for patients it may frequently be necessary to begin with a dosage of from about 2 to about 70 mg per day and when the condition is under control to reduce the dosage as low as from about 0.1 to about 10 mg per day. The exact dosage will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

15

20

Generally, the compounds of the present invention are dispensed in unit dosage form comprising from about 0.1 to about 100 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

25

Usually, dosage forms suitable for oral, nasal, pulmonary or transdermal administration comprise from about 0.001 mg to about 100 mg, preferably from about 0.01 mg to about 50 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

Any novel feature or combination of features described herein is considered essential to this invention.

30

#### EXAMPLES

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which however, are not to be construed as limiting.

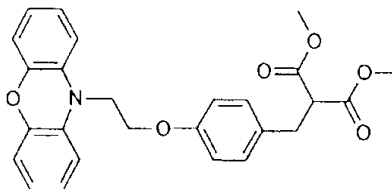
The structures of the compounds are confirmed by either elemental analysis (MA) nuclear magnetic resonance (NMR) or mass spectrometry (MS). NMR shifts ( $\delta$ ) are given in parts per million (ppm) and only selected peaks are given. mp is melting point and is given in  $^{\circ}\text{C}$ . Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se.

Abbreviations:

TLC:	thin layer chromatography
DMSO:	dimethylsulfoxide
15 CDCl <sub>3</sub> :	deuterated chloroform
DMF:	N,N-dimethylformamide
min:	minutes
h:	hours

20

EXAMPLE 1



25 2-[2-Phenoxazine-10-yl-ethoxy]-benzyl]-malonic acid dimethyl ester

---

a)

A solution of benzyloxybenzaldehyde (10.6 g, 50.0 mmol) and dimethyl malonate (6.6 g, 50.0 mmol) in benzene (100 mL) containing a catalytic quantity of piperidinium acetate was refluxed in a Dean-Stark trap for 16 h. After cooling to room temperature, the solution was concentrated. The residue was crystallised from ethyl acetate/heptane to give 14.5 g (90%) of 2-

30

(4-benzyloxy-benzylidene)-malonic acid dimethyl ester: mp 134-135°C. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.82 (s, 3H), 3.86 (s, 3H), 5.08 (s, 2H), 6.95 (d, 2H), 7.30-7.45 (m, 7H), 7.70 (s, 1H).

5 b)

A solution of 2-(4-benzyloxy-benzylidene)-malonic acid dimethyl ester (14,5 g, 44.5 mmol) in methanol (300 mL) was hydrogenated at 3 atm. in the presence of 5% palladium on charcoal (1.1 g). The solution was filtered, and the filtrate evaporated under a vacuum to give 9.2 g (77%) of 2-(4-hydroxy-benzyl)-malonic acid dimethyl ester: <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.15 (d, 2H), 3.65 (t, 1H), 3.70 (s, 6H), 6.70 (d, 2H), 7.05 (d, 2H).

10

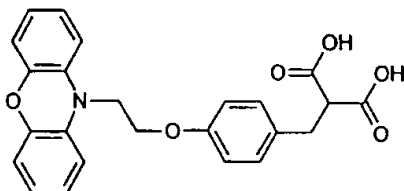
c)

Under a nitrogen atmosphere, 2-phenoxazin-10-yl-ethanol (340 mg, 1.5 mmol), tributylphosphine (455 mg, 2.25 mmol) and 2-(4-hydroxy-benzyl)-malonic acid dimethyl ester (357 mg, 1.5 mmol) were successively dissolved in dry benzene (20 mL). Solid azodicarboxylic dipiperidide (ADDP) (567 mg, 2.25 mmol) was added under stirring at 0°C to the solution. After 10 min, the reaction mixture was brought to room temperature and the stirring was continued for 2h. Heptane (10 mL) was added to the reaction mixture and dihydro-ADDP separated out was filtered off. After evaporation of the solvent the product was purified by flash chromatography gradiating from toluen to toluen/ethyl acetate (19:1). The title compound was isolated as a crystalline product (325 mg, 48%): mp 100-101°C; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ 3.15 (d, 2H), 3.62 (t, 1H), 3.68 (s, 6H), 3.95 (t, 2H), 4.15 (t, 2H), 6.58-6.70 (m, 6H), 6.75-6.84 (m, 4H), 7.10 (d, 2H)

20

25

## EXAMPLE 2



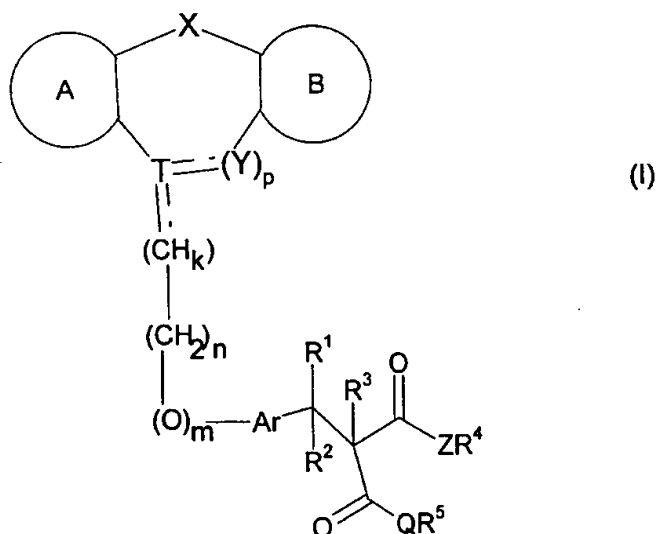
30 2-[4-(2-Phenoxazine-10-yl-ethoxy)-benzyl]-malonic acid , disodiumsalt

---

A 1 N aqueous solution of sodium hydroxide (3 mL) was added to a solution of 2-{4-(2-phenoxazine-10-yl-ethoxy)-benzyl]-malonic acid dimethyl ester (150 mg, 0.3 mmol) in a mixture of methanol (3 mL) and tetrahydrofuran (3 mL). The mixture was stirred for 64 h at room temperature. The title compound (95 mg, 72%) was isolated by filtration and washed with a mixture of MeOH/THF: mp 303-307°C; <sup>1</sup>H NMR (300 MHz, D<sub>2</sub>O): δ 2.96 (d, 2H), 3.35 (t, 1H), 3.75-3.95 (bs, 2H), 4.18 (m, 2H), 6.55-6.90 (m, 10H), 7.15 (d, 2H).

## Claims:

1. A compound of formula (I)



5

- wherein ring A and ring B, fused to the ring containing X and T, independently of each other represents a 5-6 membered cyclic ring, optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro, cyano, formyl, or C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl, C<sub>1-12</sub>-alkoxy, aryloxy, arylalkyl, arylalkoxy, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyC<sub>1-12</sub>-alkyl, amino, acylamino, C<sub>1-12</sub>-alkyl-amino, arylamino, arylalkylamino, amino-C<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C<sub>1-12</sub>-alkoxyC<sub>1-12</sub>-alkyl, aryloxyC<sub>1-12</sub>-alkyl, arylalkoxyC<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkylthio, thioC<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkoxycarbonylamino, aryloxycarbonylamino, arylalkoxycarbonylamino, bicycloalkyl, (C<sub>3-6</sub>-cycloalkyl)C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-dialkylamino, C<sub>1-6</sub>-alkylsulfonyl, C<sub>1-6</sub>-monoalkylaminosulfonyl, C<sub>1-6</sub>-dialkylaminosulfonyl, arylthio, arylsulfonyl, C<sub>1-6</sub>-monoalkylaminocarbonyl, C<sub>1-6</sub>-dialkylaminocarbonyl, -COR<sup>6</sup> or -SO<sub>2</sub>R<sup>7</sup>, wherein R<sup>6</sup> and R<sup>7</sup> independently of each other are selected from hydroxy, halogen, perhalomethyl, C<sub>1-6</sub>-alkoxy or amino optionally substituted with one or more C<sub>1-6</sub>-alkyl or perhalomethyl; or aryl, wherein the aryl optionally can be substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or heteroaryl, wherein the heteroaryl optionally can be substituted with halogen, amino hydroxy, C<sub>1-6</sub>-alkyl or

20

C<sub>1-6</sub>-alkoxy; or heterocyclyl, wherein the heterocyclyl optionally can be substituted with halogen, amino, hydroxy, C<sub>1-6</sub>-alkyl or C<sub>1-6</sub>-alkoxy,

- X is -O-, -S- or -(CHR<sup>8</sup>)- wherein R<sup>8</sup> is hydrogen, halogen, hydroxy, nitro, cyano, formyl, C<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkoxy, aryl, aryloxy, arylalkyl, arylalkoxy, heterocyclyl, heteroaryl, heteroarylalkyl, heteroaryloxy, heteroarylalkoxy, acyl, acyloxy, hydroxyalkyl, amino, acylamino, C<sub>1-12</sub>-alkyl-amino, arylamino, arylalkylamino, aminoC<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkoxycarbonyl, aryloxycarbonyl, arylalkoxycarbonyl, C<sub>1-12</sub>-alkoxyC<sub>1-12</sub>-alkyl, aryloxyC<sub>1-12</sub>-alkyl, arylalkoxyC<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkylthio, thioC<sub>1-12</sub>-alkyl, C<sub>1-12</sub>-alkoxycarbonylamino, aryloxycarbonylamino, arylalkoxycarbonylamino, -COR<sup>9</sup> or -SO<sub>2</sub>R<sup>10</sup>, wherein R<sup>9</sup> and R<sup>10</sup> independently of each other are selected from hydroxy, halogen, C<sub>1-6</sub>-alkoxy, amino optionally substituted with one or more C<sub>1-6</sub>-alkyl, perhalomethyl or aryl;

T is N or CR<sup>14</sup>, wherein R<sup>14</sup> is hydrogen, C<sub>1-12</sub>-alkoxy, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl, aryl or arylalkyl;

- Y is C, O, S, CO, SO, SO<sub>2</sub> or NR<sup>11</sup>, wherein R<sup>11</sup> is hydrogen, C<sub>1-6</sub>-alkyl;

k is 1 or 2;

$\text{---}$  represents a single or a double bond;

- Ar represents arylene, heteroarylene, or a divalent heterocyclic group each of which can optionally be substituted with one or more halogen, C<sub>1-6</sub>-alkyl, amino, hydroxy, C<sub>1-6</sub>-alkoxy or aryl;

- R<sup>1</sup> represents hydrogen, hydroxy, halogen, C<sub>1-12</sub>-alkoxy, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl or arylalkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

R<sup>2</sup> represents hydrogen, hydroxy, halogen, C<sub>1-12</sub>-alkoxy, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl or arylalkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R<sup>2</sup> forms a bond together with R<sup>3</sup>;

R<sup>3</sup> represents hydrogen, hydroxy, halogen, C<sub>1-12</sub>-alkoxy, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl, acyl or arylalkyl; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano; or R<sup>3</sup> forms a bond together with R<sup>2</sup>;

- 5 R<sup>4</sup> represents hydrogen, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- 10 R<sup>5</sup> represents hydrogen, C<sub>1-12</sub>-alkyl, C<sub>4-12</sub>-alkenynyl, C<sub>2-12</sub>-alkenyl, C<sub>2-12</sub>-alkynyl, aryl, arylalkyl, heterocyclyl, heteroaryl or heteroarylalkyl groups; optionally substituted with one or more halogen, perhalomethyl, hydroxy, nitro or cyano;

- 15 Z represents oxygen or NR<sup>12</sup>, wherein R<sup>12</sup> represents hydrogen C<sub>1-12</sub>-alkyl, aryl, hydroxyC<sub>1-12</sub>-alkyl or arylalkyl groups or when Z is NR<sup>12</sup>, R<sup>4</sup> and R<sup>12</sup> may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C<sub>1-6</sub>-alkyl;

- 20 Q represents oxygen or NR<sup>13</sup>, wherein R<sup>13</sup> represents hydrogen C<sub>1-12</sub>-alkyl, aryl, hydroxyC<sub>1-12</sub>-alkyl or arylalkyl groups or when Q is NR<sup>13</sup>, R<sup>5</sup> and R<sup>13</sup> may form a 5 or 6 membered nitrogen containing ring, optionally substituted with one or more C<sub>1-6</sub>-alkyl;


n is an integer ranging from 0 to 3;

m is an integer ranging from 0 to 1;

p is an integer ranging from 0 to 1;

- 25 or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

- 30 2. A compound according to claim 1 wherein ring A and ring B, fused to the ring containing X and T independently of each other represents a 5-6 membered cyclic ring, optionally substituted with halogen, C<sub>1-6</sub>-alkyl or aryl, wherein the aryl can be substituted with one or more halogen or C<sub>1-6</sub>-alkyl; or heterocyclyl, wherein the heterocyclyl can be substituted with C<sub>1-6</sub>-alkyl.

3. A compound according to any one of the preceding claims wherein ring A and ring B, fused to the ring containing X and T independently of each other represents a 5-6 membered cyclic ring.
- 5 4. A compound according to any one of the preceding claims wherein ring A and ring B, fused to the ring containing X and T independently of each other represents aryl.
5. A compound according to any one of the preceding claims wherein X is O.
- 10 6. A compound according to any one of the preceding claims wherein T is N.
7. A compound according to any one of the preceding claims wherein k is 2.
8. A compound according to any one of the preceding claims wherein  represents a  
15 single bond.
9. A compound according to any one of the preceding claims wherein Ar represents arylene.
10. A compound according to any one of the preceding claims wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup>  
20 represents hydrogen.
11. A compound according to any one of the preceding claims wherein R<sup>4</sup> and R<sup>5</sup> represents hydrogen or methyl.
- 25 12. A compound according to any one of the preceding claims wherein Z and Q represents O.
13. A compound according to any one of the preceding claims wherein n is 1.
14. A compound according to any one of the preceding claims wherein m is 1.  
30
15. A compound according to any one of the preceding claims wherein p is 0.
16. The compound according to claim 1 which is
- 35 2-{4-(2-Phenoxazine-10-yl-ethoxy)-benzyl]-malonic acid dimethyl ester,

2-[4-(2-Phenoxazine-10-yl-ethoxy)-benzyl]-malonic acid;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

5

17. A pharmaceutical composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

10 18. A composition according to claim 17 in unit dosage form, comprising from about 0.05 to about 100 mg, preferably from about 0.1 to about 50 mg of the compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof.

15 19. A pharmaceutical composition useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

20 20. A pharmaceutical composition useful in the treatment and/or prevention of diabetes and/or obesity, the composition comprising, as an active ingredient, a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

25 21. A pharmaceutical composition according to any one of the claims 17-20 for oral, nasal, transdermal, pulmonary, or parenteral administration.

22. A method for the treatment of ailments, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding  
30 compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding claims 17-21.

23. A method for the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR), the method  
35 comprising administering to a subject in need thereof an effective amount of a compound

according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding claims 17-21.

24. A method for the treatment and/or prevention of diabetes and/or obesity, the method comprising administering to a subject in need thereof an effective amount of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof, or of a composition according to any one of the preceding claims 17-21.

25. The method according to claims 22, 23 or 24, wherein the effective amount of the compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt or ester thereof is in the range of from about 0.05 to about 100 mg per day, preferably from about 0.1 to about 50 mg per day.

26. Use of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament.

27. Use of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament useful in the treatment and/or prevention of conditions mediated by nuclear receptors, in particular the Peroxisome Proliferator-Activated Receptors (PPAR).

28. Use of a compound according to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treatment and/or prevention of diabetes and/or obesity.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00189

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 265/38, A61K 31/538, A61P 3/10, A61P 3/04  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 9919313 A1 (DR. REDDY'S RESEARCH FOUNDATION ET AL), 22 April 1999 (22.04.99), page 1, line 24 - line 27; page 2, line 1 - line 6; page 37 - page 50, examples --	1-28
P,X	WO 9920614 A1 (DR. REDDY'S RESEARCH FOUNDATION ET AL), 29 April 1999 (29.04.99), page 1, line 23 - line 28; page 2, line 1 - line 15; page 42 - page 76, examples --	1-28
P,X	WO 9938850 A1 (DR. REDDY'S RESEARCH FOUNDATION), 5 August 1999 (05.08.99), page 1, line 27 - line 28; page 2, line 1 - line 20; page 43 - page 66, examples --	1-28

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

18 August 2000

Date of mailing of the international search report

22-08-2000

Name and mailing address of the ISA/  
Swedish Patent Office  
Box 5055, S-102 42 STOCKHOLM  
Facsimile No. +46 8 666 02 86

Authorized officer

Nebil Gecer/ELY  
Telephone No. +46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00189

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9908501 A2 (DR. REDDY'S RESEARCH FOUNDATION ET AL), 25 February 1999 (25.02.99), page 1, line 20 - line 29; page 2, line 1 - line 15; page 50 - page 90, examples --	1-28
X	WO 9916758 A1 (DR. REDDY'S RESEARCH FOUNDATION ET AL), 8 April 1999 (08.04.99), page 1, line 21 - line 28; page 2, line 1 - line 11; page 42 - page 62, examples --	1-28
X	EP 0903343 A1 (SSP CO., LTD.), 24 March 1999 (24.03.99), page 2, line 35 - line 43; page 24 - page 43, tables 1-20 --	1-28
X	WO 9604260 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96), page 2, line 1 - line 18; page 13 - page 25, examples --	1-28
X	WO 9604261 A1 (SMITHKLINE BEECHAM PLC), 15 February 1996 (15.02.96), page 2, line 1 - line 18; page 12 - page 24, examples --	1-28
X	WO 9725042 A1 (SMITHKLINE BEECHAM P.L.C.), 17 July 1997 (17.07.97), page 2, line 6 - line 21; page 18 - page 31, examples --	1-28
X	STN International, File CAPLUS, CAPLUS accession no. 1998:430714. Document no. 129:108904, Mitsui Petrochemical Industries, Ltd.: "Preparation of hydroxybenzoic acids, their use as cell adhesion inhibitors, and their pharmaceutical compositions"; & JP,A210182550, 19980707 --	1-28

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 00/00189

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 9731907 A1 (GLAXO GROUP LIMITED), 4 Sept 1997 (04.09.97)  -- -----	1-28

## INTERNATIONAL SEARCH REPORT

International application No.  
**PCT/DK00/00189****Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **22-25**  
because they relate to subject matter not required to be searched by this Authority, namely:  
**See extra sheet\***
2. ☒ Claims Nos.: **1-15, 17-28**  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
**See extra sheet\*\***
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK00/00189

\*Claims 22-25 are directed to methods of treatment of the human or animal body by therapy methods practised on the human or animal body (see PCT, Rule 39.1 (iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

\*\*The claims are too broadly formulated to permit a meaningful search over the whole of the claimed scope. Furthermore, the claims are only partly supported by the examples given in the descriptive part of the application. Guided by the spirit of the application the search was carried out mainly on the basis of the exemplified compounds (PCT Art. 6)

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/DK 00/00189

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	9919313	A1	22/04/99	NONE		
WO	9920614	A1	29/04/99	AU	1120699 A	10/05/99
WO	9938850	A1	05/08/99	NONE		
WO	9908501	A2	25/02/99	AU	1120599 A	08/03/99
WO	9916758	A1	08/04/99	NONE		
EP	0903343	A1	24/03/99	CN	1215051 A	28/04/99
				JP	11158144 A	15/06/99
WO	9604260	A1	15/02/96	AP	9700918 D	00/00/00
				AU	697545 B	08/10/98
				AU	1006199 A	04/03/99
				AU	3382695 A	04/03/96
				BG	101180 A	30/04/98
				BR	9508468 A	25/11/97
				CA	2196079 A	15/02/96
				CN	1158123 A	27/08/97
				CZ	9700254 A	17/09/97
				EP	0772605 A	14/05/97
				FI	970357 A	26/03/97
				GB	9415330 D	00/00/00
				HU	76637 A	28/10/97
				IL	114759 D	00/00/00
				IL	125525 D	00/00/00
				JP	10503508 T	31/03/98
				NO	970373 A	18/03/97
				NZ	292125 A	25/11/98
				PL	318766 A	07/07/97
				SK	12297 A	06/08/97
				TR	960096 A	00/00/00
				WO	9604261 A	15/02/96
				GB	9425599 D	00/00/00
				GB	9509923 D	00/00/00
				GB	2289999 A	06/12/95
				GB	9501323 D	00/00/00

**INTERNATIONAL SEARCH REPORT**  
Information on patent family members

International application No.  
PCT/DK 00/00189

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9604261 A1	15/02/96	AP 9700918 D	00/00/00
		AU 697545 B	08/10/98
		AU 1006199 A	04/03/99
		AU 3382695 A	04/03/96
		BG 101180 A	30/04/98
		BR 9508468 A	25/11/97
		CA 2196079 A	15/02/96
		CN 1158123 A	27/08/97
		CZ 9700254 A	17/09/97
		EP 0772605 A	14/05/97
		FI 970357 A	26/03/97
		GB 9415330 D	00/00/00
		HU 76637 A	28/10/97
		IL 114759 D	00/00/00
		IL 125525 D	00/00/00
		JP 10503508 T	31/03/98
		NO 970373 A	18/03/97
		NZ 292125 A	25/11/98
		PL 318766 A	07/07/97
		SK 12297 A	06/08/97
		TR 960096 A	00/00/00
		WO 9604260 A	15/02/96
		GB 9425599 D	00/00/00
		GB 9509923 D	00/00/00
WO 9725042 A1	17/07/97	AP 9801272 D	00/00/00
		AU 1439797 A	01/08/97
		AU 4839196 A	02/10/96
		BG 102668 A	30/04/99
		BR 9706968 A	06/04/99
		CA 2242632 A	17/07/97
		CN 1212622 A	31/03/99
		CZ 9802163 A	17/02/99
		EP 0815091 A	07/01/98
		EP 0879053 A	25/11/98
		GB 9600464 D	00/00/00
		HU 9900560 A	28/07/99
		IL 125106 D	00/00/00
		JP 10511977 T	17/11/98
		NO 974170 A	07/11/97
		NO 983147 A	08/09/98
		PL 327731 A	21/12/98
		SK 92598 A	11/01/99
		ZA 9700171 A	24/07/98

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/DK 00/00189

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9731907 A1	04/09/97	AP 9700935 D	00/00/00
		AU 2093597 A	16/09/97
		BG 102792 A	31/08/99
		CA 2247443 A	04/09/97
		CN 1218460 A	02/06/99
		CZ 9802750 A	13/01/99
		EP 0888317 A	07/01/99
		GB 9604242 D	00/00/00
		HR 970110 A	30/04/98
		IL 125796 D	00/00/00
		NO 983940 A	27/10/98
		PL 328871 A	01/03/99
		SK 116398 A	13/04/99
<hr/>			

